Rijks Universiteit Groningen

Risk factors for renal abnormalities in a nondiabetic population

PROEFSCHRIFT

ter verkrijging van het doctoraat in de Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de Rector Magnificus, dr. D.F.J. Bosscher,
in het openbaar te verdedigen op woensdag 14 november 2001
om 14.15 uur
door

Sara Johanna Pinto-Sietsma
geboren op 6 december 1968 te Amsterdam

Promotores:	Prof. dr. P.E. de Jong Prof. dr. D. de Zeeuw Prof. dr. M. Paul
Referent:	Dr. W.M.T. Janssen
Beoordelingscommissie:	Prof. dr. C.E. Mogensen Prof. dr. C.D.A. Stehouwer Prof. dr. D.E. Grobbee

ISBN 90-9015223-7

ALS IK LATER GROOT BEN….

Aylon (5 jaar): ”Als ik later groot ben word ik dokter en piloot, dan kan ik alle mensen met hoogtevrees helpen.”

Soesja (2 jaar): “Als ik later groot ben ga ik met Aylon trouwen. Wanneer word ik nou groot? Het duurt zo lang!”

Op gedragen aan: Mijn ouders
voor: Yigal, Aylon en Soesja

Paranimfen: Drs. M. Heeringa-Karreman
Drs. D.I. Vos

Financial support by the Netherlands Kidney Foundation and the Groningen University Institute for Drug Exploration (GUIDE), AstraZeneca BV, Bristol-Myers Squibb BV, GlaxoSmithKline, Janssen-Cilag BV, Knoll BV, Novo Nordisk Farma BV, Bayer B.V., Novartis Pharma BV, Merck Sharp and Dohme BV, Sanofi~Synthelabo, Aventis Pharma bv and Pfizer bv for publication of this thesis are greatly acknowledged.

Typesetting and lay-out by S.J. Pinto-Sietsma
Printing by Drukkerij Meesters Media bv, Maastricht

Coverdesign: by S.J. Pinto-Sietsma

The studies presented in this thesis were performed at the Dept. of Internal Medicine, Division of Nephrology, University Hospital Groningen, Groningen, The Netherlands, General Practionaires Laboratory, Groningen, The Netherlands, and Department of Clinical Pharmacology and Toxicology, and Department of Internal Medicine, Division of Nephrology, University Hospital Benjamin Franklin, Berlin, Germany.

-Contents-

-Introduction-

Early renal function abnormalities have mainly been investigated in diabetic subjects. This because diabetic subjects are being followed for their diabetic disease and thereby it has been shown that they are prone to develop renal function loss[1].

From human and animal experimental research, it has been shown that an increased glomerular filtration rate (GFR), called hyperfiltration or elevated filtration, can occur prior to renal function loss[2-4]. This hyperfiltration is viewed of as nephrons compensating, by increasing their GFR, for nephrons that have a lower GFR or have lost their ability to function at all[4,5]. Whether nondiabetic subjects also have this elevated filtration, and whether this also precedes renal function loss is still unknown. This thesis tries to identify nondiabetic subjects prone to develop renal damage in an early phase.

Healthy nondiabetic subjects are not being followed for renal disease and they only come to medical attention after the development of renal damage. Therefore, it is difficult to detect renal abnormalities in healthy nondiabetic subjects in an early phase. In particular, since an easy screening method is not available yet. Serum creatinine has often been used as a screening method, but it has the drawback that it overestimates renal function in the lower ranges[6]. Therefore, more easy methods to screen for renal functional abnormalities are necessary. It is known from diabetes research, that small amounts of albumin in the urine called "microalbuminuria (30-300 mg/24hr)" are an important early sign of incipient diabetic nephropathy[7,8]. Urinary albumin is easy to obtain and is relatively easy to measure. Nowadays effort is being put to try and measure albumin by dipstick, which would make it an even easier tool to screen for early renal abnormalities.

Unfortunately, it is not known until now, if microalbuminuria is also an important early sign of renal abnormalities in nondiabetic subjects. In other words, can we use this easy screening method for the total population? In chapter 1 of this thesis we try to shed some light on this issue, by investigating the relationship between different amounts of urinary albumin excretion and renal function and whether a relation between albuminuria and renal function can be observed, similar as in diabetes.

Another way to identify subjects at risk for renal function loss in an early phase is to gain insight in the possible risk factors related to renal abnormalities, the 'renal' risk factors. Of major interest are subjects with an elevated filtration, since they might be prone to develop renal function loss, as mentioned before. By paying more attention to 'renal' risk factors, subjects at risk for renal damage can be identified and intervention can be started in an early phase.

We found a similar relation between albuminuria and renal function in nondiabetic subjects as in diabetic subjects, suggesting that possibly risk factors related to diabetic renal disease could also be of importance for non-diabetic renal disease. Chapters 2, 3, 4 and 5 try to identify whether smoking, obesity, or blood pressure are such 'renal' risk factors.

Another possible important risk factor for renal disease is endothelin an endothelium-derived vasoconstrictor[9]. This substance has been associated not only with renal functional abnormalities[10,11], but also with albuminuria[12,13], smoking[14,15], obesity[16], and hypertension[17] all 'renal' risk factors investigated in this thesis. We hypotesize, that endothelin plays an important key role in renal disease.

Most of the literature on endothelin has focussed on hypertension. Therefore, as an introductory, Chapter 6 discusses the role of endothelin in hypertension and renal disease.

If endothelin would play a key role in renal disease, by what mechanisms could this be? All the risk factors investigated in this thesis are related to endothelial dysfunction[18-20], and since the risk factors in this thesis are related to endothelin, it follows that endothelin could be related to endothelial dysfunction.

Chapter 7 discusses the possibility of endothelin to induce endothelial dysfunction by it self. Hereby introducing endothelin as a key player in the process in which risk factors together with endothelial dysfunction lead to end-organ damage.

The question remains however whether endothelin is causally involved in renal disease, or whether it is secondary to it. One way to gain some insight into the cause-effect relationship between endothelin and renal disease is through animal and human genetic studies. Chapter 8, therefore, dis-

cusses the possibility that genetic variation in the endothelin-1 gene is related to renal abnormalities. This might indicate that endothelin could be a major contributor to renal disease.

Finally, the summary summarizes the observed findings and will put them in to perspective. Furthermore, the implications for the future will be addressed in this chapter.

References

1. Knowles HC Jr: Magnitude of the renal failure problem in diabetic patients. *Kidney Int* 1 Suppl:2-7, 1974
2. Rudberg S, Persson B, Dahlquist G: Increased glomerular filtration rate as a predictor of diabetic nephropathy- an 8-year prospective study. *Kidney Int* 41:822-828, 1992
3. Hostetter TH, Rennke HG, Brenner BM: The case for intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. *Am J Med* 72:375-380, 1982
4. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM: Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol* 241:F85-F93, 1981
5. Hostetter TH, Rennke HG, Brenner BM: Compensatory renal hemodynamic injury: A final common pathway of residual nephron destruction. *Am J Kidney Dis* 1:310-314, 1982
6. Lindeman RD: Assessment of renal function in the old. Special considerations. *Clin Lab Med* 13:269-277, 1993
7. Viberti GC, Hill RD, Jarret RJ, Argyropoulos A, Mahmud U, Keen H: Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet* I:1430-1432, 1982
8. Mogensen CE: Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 310:356-360, 1984
9. Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayaski M, Mitsui Y, Yazaki Y, Goto K, Masaki T: A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 332:411-415, 1988
10. Orisio S, Benigni A, Bruzzi I, Corna D, Perico N, Zoja C, Benatti L, Remuzzi G: Renal endothelin gene expression is increased in remnant kidney and relates with disease progression. *Kidney Int* 43:354-358, 1993
11. Miller WL, Redfield MM, Burnett JC Jr: Integrated cardiac, renal and endocrine actions of endo-

thelin. *J Clin Invest* 83:317-320, 1989
12. Collier A, Leach JP, McLellan A, Jardine A, Morton JJ, Small M: Plasma endothelin like immunoreactivity levels in IDDM patients with microalbuminuria. *Diabetes Care* 15:1038-1040, 1992
13. Ferri C, Bellini C, Desideri G, Mazzocchi C, De Siati L, Santucci A: Elevated plasma and urinary endothelin-1 levels in human salt-sensitive hypertension. *Clin Sci* 93:35-41, 1997
14. Gambaro G, Verlato F, Budakovic A, Casara D, Saladini G, Del Prete D, Bertaglis G, Masiero M, Checchetto S, Baggio B: Renal impairment in chronic cigarette smokers. *J Am Soc Nephrol* 9:562-567, 1998
15. Haak T, Jungmann E, Raab C, Usadel KH: Elevated endothelin-1 levels after cigarette smoking. *Metabolism* 43:267-269, 1994
16. Ferri C, Bellini C, Desideri G, Di Francesco L, Baldoncini R, Santucci A, De Mattia G: Plasma endothelin-1 levels in obese hypertensive and normotensive men. *Diabetes* 44:431-436, 1995
17. Kohno M, Yasunari K, Murakawa KI, Yokokawa K, Horio T, Fukui T, Takeda T: Plasma immunoreactive endothelin in essential hypertension. *Am J Med* 88:614-618, 1990
18. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK, Deanfield JE: Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 340:1111-1115, 1992
19. Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, Baron AD: Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. *J Clin Invest* 97:2601-2610, 1996
20. Taddei S, Salvetti A: Pathogenetic factors in hypertension. Endothelial factors. *Clin Exp Hypertens* 18:323-335, 1996